

Case of Epileptic Encephalopathy with Mental Retardation Due to KIAA2022 Gene Impairment (Mental Retardation X-Linked 98)

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Abstract

The article describes the case of X-linked mental retardation-98 in 21-years-old young male with clinical characteristics of epileptic encephalopathy, mental retardation and autistic features. Was identified previously not described variant of *de novo* microdeletion in KIAA2022 (NEXMIF) gene on chromosome X: g.73962680_73962683del ENST00000055682.6: c.1713_1716del ENSP00000055682.5: p.Ser571ArgfsTer13 in result of microdeletion of four nucleotides caused reading frame shift error. Patient demonstrated seizure onset from the age of 1 year and 2 month with propulsive epileptic spasms and later the wide polymorphism of seizure types: propulsive tonic spasms isolated and in series, myoclonic, tonic axial and axorhizomelic seizures, ophthalmotonic seizures, asymmetric tonic versive, global tonic and tonic-vibratory seizures, tonic-autonomic seizures with dyspnoe and acrocyanosis, dialeptic seizures, asymmetric tonic seizures with pharyngo-oral automatisms, peak-wave stupor episodes with atypical absences, rarely - bilateral tonic-clonic seizures. EEG video monitoring demonstrated multifocal epileptiform spike-wave activity, secondary bilateral synchronization with diffuse spreading. The case was pharmacoresistant, but cannabidiol treatment caused positive effect in significant decreasing of epileptiform discharges and seizures.

Keywords: *Epileptic Encephalopathy; Mental Retardation Non-Syndromic X-Linked; Mental Retardation X-Linked 98; MRX98; KIAA2022 Gene*

Introduction

There is growing evidence that epileptic encephalopathies, developmental delay in children and autistic behavior are often genetically determined. X chromosome contains a significant proportion of genes responsible for development, as well as those that play role in epileptogenesis. On the present time OMIM database had contained 51 entries of non-syndromic X-linked mental retardations (ACSL4, ARX, BRWD3, CLCN4, CXorf56, DDX3X, DLG3, DUPXp11.22, FRMPD4, FTSJ1, GDI1, GRIA3, HCFC1, IL1RAPL1, IQSEC2, KIF4A, KLHL15, MID2, MRX14, MRX2, MRX20, MRX23, MRX42, MRX45, MRX46, MRX50, MRX53, MRX73, MRX77, MRX81, MRX82, MRX84, MRX88, MRX89, MRX91, MRX92, MRX95, NEXMIF (KIAA2022), OGT, PAK3, RAB39B, RLIM, RPS6KA3, SLC9A7, SYP, THOC2, TSPAN7, USP27X, USP9X, USP9X and ZNF711 genes) and 47 entries of syndromic X-linked mental retardations (AFF2, AP1S2, ARX, ATP6AP2, CASK, CLIC2, CNKSR2, CUL4B, EIF2S3, FGD1, FMR1, GRIA3, HNRNPH2, HS6ST2, HUWE1, IGBP1, KDM5C, LAS1L, MECP2, MRXS12, MRXS17, MRXS7, MRXS9, MRXSA, MRXSAB, MRXSCS, MRXSMP, MSL3, NONO, OPHN1, PHF6, PHF8, POLA1, PQBP1, PRPS1, PRS, RAB39B, RBMX, RPL10, SHROOM4, SLC9A6, SMS, TAF1, UBE2A, UPF3B, ZC4H2 and ZDHHC9) and the database is constantly expanding. Different mutation in some genes could cause different phenotypic series. For example, mental retardation X-linked (MRX) ARX-related contains MRX29, MRX32, MRX33,

MRX38, MRX43, MRX52, MRX54, MRX76 and MRX87 phenotypes. At the time of February 2020 are classified 107 genetic variants of X-linked mental retardation [1].

X-linked mental retardation-98 (MRX98, OMIM#300912) is a neurodevelopmental disorder characterized by delayed psychomotor and speech development, behavioral abnormalities and often early-onset seizures. MRX98 is caused by hemizygous or heterozygous mutation in the KIAA2022 gene (NEXMIF; 300524) on chromosome Xq13 [2,3].

Materials and Methods

At the period of 2005 - 2020 the boy grown to a young man with clinical characteristics of epileptic encephalopathy with mental retardation with newly identified *de novo* microdeletion of four nucleotides in KIAA2022 gene was investigated and treated. Clinical, anamnesis and laboratory data were analyzed. Dynamical video-EEG monitoring investigations were performed by "Encephalan-Video" RM-19/26 (Medicom MTD, Russia) and "NeuroScope" NS432, NS25A, NS450A (Biola, Russia). Magnetic resonance visualization had obtain (Siemens Magnetom Aera 1.5 Tl, Germany, Signa Infinity 1.5 Tl General Electric, USA). At 2019 DNA sequencing was obtained (Next Generation Sequencing on platform Illumina NovaSeq 6000, USA).

Results

We present the case of young male N. 21-years-old with clinical characteristics of epileptic encephalopathy with mental retardation who had newly identified *de novo* microdeletion in KIAA2022 gene. Previously not described variant - chromosome X: g.73962680_73962683del ENST00000055682.6: c.1713_1716del ENSP00000055682.5: p.Ser571ArgfsTer13 in result of microdeletion of four nucleotides caused reading frame shift error with and loss of function in KIAA2022 (NEXMIF) gene.

Anamnesis: The boy from the fourth pregnancy (two pregnancies - medical abortion and one - spontaneous abortion at short term). Pregnancy with toxicosis, risk of interruption, mycoplasmic and ureaplasma infection at the second trimester, edemas of low extremities at the third trimester. Caesarian section at 36 week of gestation (anatomical narrow pelvis). Was born with the weight of 3000 g., length of 51 cm., Apgar scale 8/9 degrees. Prolonged jaundice of newborns up 1 month. Muscular dystonia with prevalence of hypotonia. No family history of epilepsy. Developing of motor skills with delay: Keeps the head from 4,5 month. Have got ability to sit by himself at 1 year. At the age of 1,5 year started walking down on hands and knees. At 2 years can stand with handhold. Walking with the help at the age of 4 years. Independent walking - from the age of 5 years. Seizure onset from the age of 1 year and 2 month after intensive course of point massage, physiotherapy and swimming procedures. The first seizure type were propulsive epileptic spasms isolated and in series (nod and raising the shoulders). Increasing of seizures up 5 - 6 series for 10 - 15 spasms in serial daily and myoclonic seizures at sleep started.

Patient demonstrated the wide polymorphism of seizure types: propulsive tonic spasms isolated and in series, myoclonic seizures during sleep, tonic axial and axorhizomelic seizures, ophthalmotonic seizures, asymmetric tonic versive seizures with alternative lateralization, global tonic and tonic-vibratory seizures, tonic-autonomic seizures with dyspnoe and acrocyanosis, dialeptic seizures ("pseudoabsences"), asymmetric tonic seizures with pharyngo-oral automatism, peak-wave stupor episodes with atypical absences, rarely - bilateral tonic-clonic seizures.

In neurological status is observed: Smoothed right naso-labial folds. Pseudobulbar syndrome. Tendon reflexes from hands moderately increased S > D, patellar reflexes is torpid, achilles reflexes is preserved, D = S, Babinsky reflex D and S. Abdominal reflexes are preserved. Kyphoscoliosis phenomenon. Moderate diffuse hypotonia. Frontal ataxia. Dysmetria. Delay of psychic and speech development. Do not enter in contact and fulfill commands, autistic behavior and total alalia.

Magnetic resonance imaging revealed moderate cortical atrophy predominantly in frontal regions and moderate ventriculomegaly ex vacuo.

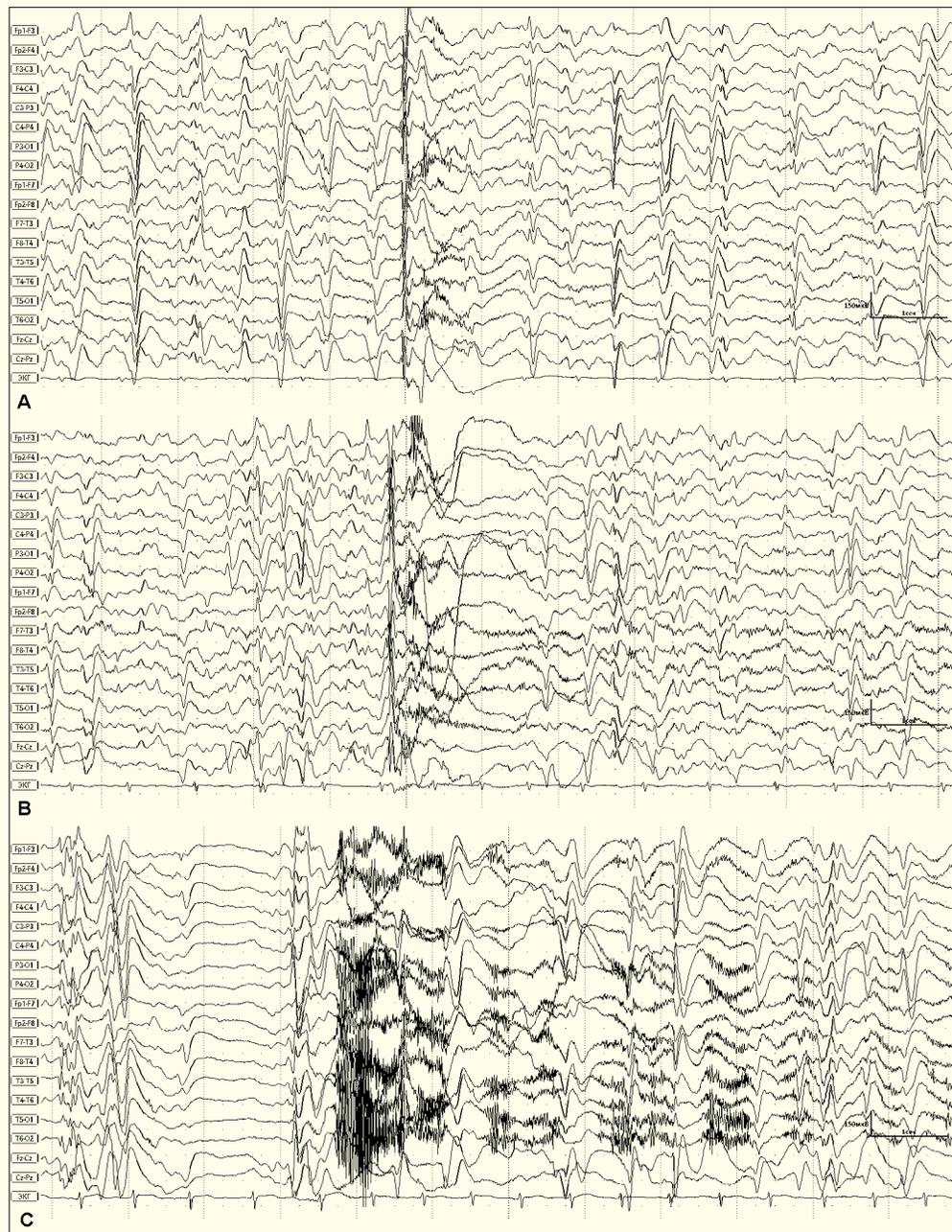


Figure 2: Patient N. at 15 years old. Ictal EEG patterns.

A: EEG of ophthalmotonic seizure with diffuse “fast activity” pattern after impressive bilateral spike-wave discharge.

B: EEG of axial tonic seizure - massive bilateral spike-wave discharge with diffuse “fast activity” pattern and electrodecrement.

C: EEG of nocturnal bilateral tonic-vibratory seizure (tonic seizure with cluster clonies) - massive myographic artifacts mask “fast activity”; subsequent sharp and slow waves accompanied cluster clonies movements.

Antiepileptic treatment until the age of five was irregular. Valproates (depakine, convulsofin, convulex) were ineffective. The child had got a complex treatment of nootropic aminoacid drugs and was conducted courses of transplantations of embryonic nervous tissues. Nootropic neuropeptide drugs caused seizure aggravation with two episodes of prolonged bilateral tonic-clonic seizures and neurological deterioration. From the age of six years - combination of valproates with ethosuximide (suxilep, petnidan) and then mesuximid (petinutin) with moderate but temporary effect. Corticosteroids were not performed because of negative attitude of the child's mother to this type of treatment. Topiramate (topamax) - no effect. At the age of ten barbiturate (benzonal) and levetiracetam (keppra) caused moderate temporary effect, but periods of seizure decreasing changed with reactivation of previous seizure frequency. Short courses of clobazam (frisium) 10 mg for 1-3 days and diazepam in rectal tubes 10 mg per rectum helps in periods of seizure increasing. From the age of fifteen accepted rufinamide (inovelon), levetiracetam (keppra) and lacosamide (vimpat) - with moderate but temporary positive effect requiring increasing doses of drugs. At present time, the 21-year-old young man receives an unauthorized in Russia drug - cannabidiol (CBD) with positive effect of significant decreasing of epileptiform discharges and seizures.

Discussion

X-linked mental retardation-98 is a neurodevelopmental disorder characterized by delayed psychomotor and speech development, behavioral abnormalities, often early-onset seizures and non-rare dysmorphic facial features, microcephaly and poor growth. Males tend to be more severely affected than females. In females is observed different penetrance and expressivity - phenotypic variability and disease manifestations results from skewed X-inactivation or cellular mosaicism [3].

At 2004 Cantagrel V, *et al.* in a family with two mentally retarded males identified a pericentric inversion $inv(X)(q13;p22)$ interrupting the KIAA2022 and P2RY8 genes. Later it was revealed that the severe mental retardation of this affected males was due to the absence of the KIAA2022 gene product [2]. Modern alternative title of KIAA2022 is neurite extension and migration factor (NEXMIF) gene [1].

Van Maldergem L., *et al.* (2013) reported about 9 affected males from 4 unrelated families with non-syndromic X-linked mental retardation with KIAA2022 gene defects. The patients had delayed psychomotor development, absent or poor speech development, often with microcephaly. Some patients demonstrated autistic behavioral features - stereotypic hand movements and repetitive behaviors. Some patients had dysmorphic features, including round face, short nose, short philtrum and esotropia. Female carriers were unaffected [4].

Kuroda Y., *et al.* (2015) described two unrelated Japanese boys with KIAA2022 mutation. Both patients had severely delayed psychomotor development apparent since early infancy, hypotonia, absent language, autistic behavior and dysmorphic features but neither patient had seizures [5].

Farach LS and Northrup H (2016) reported about 17-year-old girl with KIAA2022 mutation caused severe intellectual disability, speech limitation to a few words, autistic features and refractory epileptic seizures since one-year age. EEG showed multifocal and diffuse bilateral epileptiform discharges. The girl had short stature with poor overall growth and dysmorphic features, including thick coarse hair, bitemporal narrowing, prominent nasal bridge, brachydactyly, a single transverse palmar crease and fifth finger clinodactyly. She had undergone epilepsy surgery - corpus callosotomy, which resulted in improved seizure frequency. She was not toilet trained and had repetitive behaviors, aggression, and hyperactivity. In addition, Farach L.S. and Northrup H. noted the phenotypic similarities to males with MRX98 [6].

De Lange., *et al.* (2016) reported about 14 female patients with *de novo* heterozygous mutations in the KIAA2022 gene. Thirteen of them had no family history of a similar disorder and had mild to severe intellectual disability. In addition, the fourteenth woman was diagnosed after her two sons with intellectual disability were found to carry a KIAA2022 mutation; she had a history of seizures but with no intellectual disability. Twelve of 14 patients had intractable epilepsy with myoclonic and/or absence seizures, 11 developed

bilateral tonic-clonic seizures and five had status epilepticus. EEG abnormalities included background slowing, focal and multifocal discharges spike-waves and polyspike-waves. Most patients had refractory seizures and severe behavioral abnormalities, including autism, aggression and hyperactivity [3].

Webster, *et al.* (2017) reported 5 unrelated girls with MRX98. Patients have severe global developmental delay, poor or absent speech and early-onset intractable seizures. Additional features included hypotonia, ataxic gait, autism, attention-deficit disorder and hyperactivity, gastroesophageal reflux or constipation [7].

Lambert N., *et al.* (2018) reported about the novel NEXMIF (KIAA2022) pathogenic variant in the boy with severe autistic features, intellectual disability and epilepsy, also with his mildly affected mother [8].

In 2018 Kozhanova TV., *et al.* describes the case of KIAA2022 gene mutation in 5-year-old Russian girl with epilepsy, an obvious delay in psychomotor, speech and intellectual development, behavioral disorders and autistic traits. The DNA sequencing revealed a previously unknown *de novo* heterozygous mutation in the 3 exon of the KIAA2022 gene - p.Asp451fs [9].

Samanta D and Willis E (2020) demonstrated that KIAA2022 gene mutation could cause Jeavons (eyelid myoclonia with absence) syndrome [10].

Our case also shows the clinical variant of X-linked mental retardation-98 with epileptic encephalopathy, mental retardation and atypical autism. Epileptic syndrome considered as the case of late-onset cryptogenic spasms with later developing of Lennox-Gastaut-like phenotype and variant of severe epilepsy with multifocal independent spike-wave foci syndrome (SE-MISF). The boy have no microcephaly an no poor overall growth as it usually presented, but he have some dysmorphic facial features as round face combined with bitemporal narrowing, large ears and his mouth is usually opened. Frontal type of ataxia and hypotonia is also very typical.

Conclusion

KIAA2022 (NEXMIF) gene mutations could cause epilepsy with mental retardation and autistic features - X-linked mental retardation-98. All the children with epileptic encephalopathies, delay of psychomotor and speech development and autistic behavior need a comprehensive examination, including video EEG monitoring, good quality neuroimaging and mandatory genetic examination by new generation exomal sequencing techniques. Also, cannabidiol treatment could be helpful for therapy of pharmaco-resistant epileptic encephalopathies and could improve the quality of life for patients and their relatives.

Conflict of Interest

The authors declare that there is no conflict of interest.

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